



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 401/12</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/25711</b> <b>(43) International Publication Date:</b> 27 May 1999 (27.05.99)
<b>(21) International Application Number:</b> PCT/SE98/01984 <b>(22) International Filing Date:</b> 3 November 1998 (03.11.98) <b>(30) Priority Data:</b> 9704183-4 14 November 1997 (14.11.97) SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> COTTON, Hanna [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). LARSSON, Magnus [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MATTSON, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). <b>(74) Agent:</b> HÄLLGREN, Christer; Astra Aktiebolag, Intellectual Property, Patents, S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NEW PROCESS  <b>(57) Abstract</b>  The present invention relates to a novel process for the synthesis of 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2- pyridinyl)methyl] sulfinyl]-1H- benzimidazole, known under the generic name omeprazole. Moreover, the present invention also relates to manufacture of a pharmaceutical preparation thereof and its use in medicine. The novel process for the preparation of omeprazole, comprises the step of oxidizing 5-methoxy-2- [[(4-methoxy-3, 5-dimethyl-2- pyridinyl) methyl]thio]-1H- benzimidazole in an organic solvent with an oxidizing agent in the presence of a titanium complex and optionally in the presence of a base.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## NEW PROCESS

*Field of the invention*

5 The present invention relates to a novel process for the preparation of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. Moreover, the present invention also relates to the manufacture of a pharmaceutical preparation thereof and its use in medicine.

10 *Background of the invention and prior art*

The compound 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more  
15 general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole and therapeutically acceptable salts thereof, are described in EP 5 129. This patent also discloses a process for the preparation of omeprazole and other structurally  
20 related substituted benzimidazoles.

US 5,386,032 describes an improved process for synthesis of omeprazole. This process describes the oxidation step and a work-up procedure for omeprazole. The oxidation step utilizes m-chloroperoxybenzoic acid in a solvent system consisting of an organic solvent  
25 and an aqueous phase of constant pH. The work-up procedure includes an extraction step and precipitation of omeprazole by the addition of an alkyl formate to the aqueous phase.

Another alternative process for the manufacture of omeprazole is described in US 5,391,752. This process utilizes magnesium monoperoxyphthalate as an oxidizing agent.

Omeprazole is a sulfoxide and a chiral compound, with the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the *R* and *S*-enantiomer of omeprazole. An enantioselective process for the synthesis of the single enantiomers of omeprazole is described in WO 96/02535. The asymmetric oxidation utilizes a chiral titanium complex to induce the chirality.

In the light of the above there was still a need for a new convenient and more efficient process for the manufacture of racemic omeprazole.

#### *Summary of the Invention*

The object of the present invention is to provide a novel process for the preparation of omeprazole. In the present invention, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole is oxidized to omeprazole in an organic solvent with an oxidizing agent in the presence of a titanium complex, and optionally in the presence of a base. The present invention is further characterized in that omeprazole precipitates from the reaction mixture. Omeprazole, substantially free from titanium salts, can thereafter easily be filtered off from the reaction mixture and thereby avoiding time consuming steps, such as work up procedures including extraction. This precipitation of omeprazole from the reaction mixture is unexpected since the corresponding single enantiomers of omeprazole does not precipitate from the reaction mixture if the same reaction conditions are used.

This precipitation of omeprazole from the reaction mixture is advantageous and the present invention is the first process described for the preparation of omeprazole involving no extraction step. The precipitation of omeprazole results in a number of further advantages. Omeprazole is sensitive towards acid and over-oxidation, *i.e.* oxidation from sulfoxide to sulfone. However, since both these reactions take place in the solution phase, they are both suppressed by the fact that omeprazole precipitates from the reaction mixture. This

precipitation of omeprazole also suppresses other potential side-reactions, such as thermal decomposition of omeprazole.

The titanium complex suitable for catalysing the process of the present invention is prepared from a ligand and a titanium(IV) compound, preferably a titanium(IV)alkoxide, and optionally in the presence of additional water. An especially preferred titanium(IV)alkoxide is titanium(IV)isopropoxide or -propoxide. The amount of the titanium complex used in the present invention is not critical. An amount of less than approximately 0.50 equivalents, in proportion to the sulfide, is preferred and an especially preferred amount is 0.05 - 0.30 equivalents. However, less than 0.05 equivalents could also be used and the lower limit of 0.05 equivalents is only given for handling reasons.

The ligand used in the present invention to produce the titanium complex can be either an achiral or a chiral ligand of which the latter is preferred. Useful ligands are alcohols, such as diols, and preferably vicinal diols. The diol may be a branched or unbranched alkyl diol, or an aromatic diol. Preferred diols are esters of tartaric acid, such as ethyl esters.

The titanium complex may also be prepared by reacting titanium tetrachloride with a suitable ligand in the presence of a base.

The present invention is further characterized by that an achiral ligand or a mixture of stereoisomers, such as a mixture of enantiomers, of a chiral ligand is used. All mixtures including a racemic mixture is within the scope of the present invention.

In a preferred aspect of the present invention a racemic mixture of chiral ligands is used to prepare the titanium complex.

The oxidizing agent used is not crucial and can be selected to suit the reaction conditions and equipment used. Examples of such oxidizing agents include, but are not limited to, peroxyacides, such as m-chloroperoxybenzoic acid, and peroxides, such as cumene hydroperoxide, tert-butyl hydroperoxide and hydrogen peroxide. One advantage of the

present invention is that a less reactive and less corrosive oxidizing agent can be used to prepare omeprazole compared to those used in the prior art. The amount of oxidizing agent used according to the present invention is preferably approximately one equivalent, such as 0.9 to 1.05 equivalents, in proportion to the sulfide.

5 According to a preferred aspect of the invention, cumene hydroperoxide or tert-butyl hydroperoxide are used as oxidizing agent.

10 According to one aspect of the invention the oxidation is carried out in the presence of a base, such as 0.05 - 1.0 equivalents, preferably 0.15 - 0.3 equivalents. Optionally, the oxidation can be carried out in the absence of a base.

The base may be an inorganic or an organic base. Organic bases are preferred and especially suitable bases are amines, preferably triethylamine or N,N-diisopropyl-ethylamine. The amount of base added to the reaction mixture is not crucial.

15 The oxidation is preferably carried out in an organic solvent around room temperature or above, *e.g.* between 10 - 60°C. Suitable organic solvents are for instance toluene, ethyl acetate, and the like. Toluene is the preferred solvent.

20 The order in which the reactants, *i.e.* the titanium compound, the ligand, the base, the solvent, water, and the 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, are charged into the reaction vessel is not crucial and should be adapted to suit the equipment used. It is however preferred that all reactants are loaded into the reaction vessel before the oxidizing agent is added.

25 The preparation of the titanium complex may be performed at room temperature or at an elevated temperature and/or during a prolonged preparation time and in the presence or absence of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

According to one aspect of the present invention the titanium complex is prepared in the presence of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

An advantage of the process according to the present invention is that omeprazole precipitates from the reaction mixture without simultaneous precipitation of titanium salts. Due to this precipitation, omeprazole can be easily separated from the reaction mixture by filtration or centrifugation and thereby avoiding any time consuming work-up procedure.

The process of the present invention may also be used to produce not only omeprazole but also other substituted sulfinyl heterocyclic compounds known in the art, such as compounds with the generic names lansoprazole, pantoprazole, leminoprazole and rabeprazole.

The following example which will further illustrate the invention, but is not intended to limit the scope of the invention as defined hereinabove or as claimed below.

#### *Example*

5-Methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.7 mmol) was dissolved in toluene (70 ml). The solution was heated to 50°C and water (0.030 ml) was added. To the resulting mixture was added diethyl(D,L)-tartrate (2.02 g, 9.78 mmol) in toluene (8 ml) and titanium(IV)isopropoxide (1.33 g, 4.68 mmol). The mixture was cooled to 30°C and diisopropylethylamine (0.962 g, 7.44 mmol) was added followed by cumene hydroperoxide (8.21 g, 53.9 mmol). The mixture was stirred at 30°C for 5h and the precipitated product was filtered off and washed with toluene (12 ml). Yield: 13.1 g (81%).

## CLAIMS

1. A process for the preparation of omeprazole, comprising the step of oxidizing 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in an  
5 organic solvent with an oxidizing agent and optionally in the presence of a base characterized in that the oxidation is performed in the presence of a titanium complex.
2. A process according to claim 1, characterized in that the oxidation is performed in the presence of a base.
- 10 3. A process according to claim 1 or 2, characterized in that the titanium complex is prepared from a titanium(IV) compound and an enantiomeric mixture of chiral ligands.
4. A process according to claim 3, characterized in that the enantiomeric mixture is a  
15 racemic mixture.
5. A process according to claim 1, characterized in that the titanium complex is prepared from a titanium(IV) compound and an achiral ligand.
- 20 6. A process according to claim 1, characterized in that omeprazole precipitates from the reaction mixture.
7. A process according to claim 1, characterized in that no extraction step is used.
- 25 8. A process according to any of claims 1-7, characterized in that the titanium complex is prepared in the presence of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole.

9. A process according to any of claims 1-8, characterized in that the oxidizing agent is cumene hydroperoxide or tert-butyl hydroperoxide.
10. A process according to any of claims 1-9, characterized in that the organic solvent is  
5       toluene.
11. A process according to any of claims 1-10, characterized in that the base is triethylamine or N,N-diisopropylethylamine.
- 10   12. A pharmaceutical formulation comprising omeprazole and a pharmaceutically acceptable carrier or diluent characterized in that the omeprazole is prepared according to any of claims 1-11.
13. Omeprazole prepared by a process according to any of claims 1-11.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01984

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9602535 A1 (ASTRA AKTIEBOLAG), 1 February 1996 (01.02.96)	1-2
A	--	3-11
X	EP 0005129 A1 (AKTIEBOLAGET HÄSSLE), 31 October 1979 (31.10.79)	12-13
	-- -----	

☐ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 January 1999

Date of mailing of the international search report

19-01-1999

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson  
Telephone No. +46 8 782 25 00

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.

PCT/SE 98/01984

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0005129 A1	31/10/79	SE 0005129 T3	
		AT 100583 A	15/12/83
		AT 100683 A	15/09/83
		AT 100783 A	15/09/83
		AT 273279 A	15/09/83
		AT 374471 B	25/04/84
		AT 374472 B	25/04/84
		AT 374473 B	25/04/84
		AT 375365 B	25/07/84
		AT 389995 B	26/02/90
		AU 529654 B	16/06/83
		AU 4602779 A	18/10/79
		BG 61492 B	30/09/97
		CA 1127158 A	06/07/82
		CA 1129417 A	10/08/82
		CS 261851 B	10/02/89
		CS 261872 B	10/02/89
		CS 261873 B	10/02/89
		CS 261874 B	10/02/89
		CS 7902549 A	15/07/88
		CS 8405767 A	15/07/88
		CS 8405768 A	15/07/88
		CS 8405769 A	15/07/88
		CY 1232 A	29/06/84
		DD 142882 A	16/07/80
		DK 150510 B,C	16/03/87
		DK 151179 A	15/10/79
		DK 151802 B,C	04/01/88
		DK 420982 A	22/09/82
		FI 65067 B,C	30/11/83
		FI 70214 B,C	28/02/86
		FI 791219 A	15/10/79
		FI 832220 A	17/06/83
		HK 15284 A	02/03/84
		IE 48370 B	26/12/84
		JP 1312930 C	28/04/86
		JP 1504537 C	13/07/89
		JP 54141783 A	05/11/79
		JP 58192880 A	10/11/83
		JP 60034956 B	12/08/85
		JP 63053191 B	21/10/88
		LT 2274 A	15/12/93
		LT 2275 A	15/12/93
		LT 2276 A	15/12/93
		LT 2277 A	15/12/93
		LT 93793 R	15/12/93
		LT 93893 R	15/12/93
		LT 93993 R	15/12/93
		LT 94093 R	15/12/93
		LU 88305 A	04/05/94
		LU 88307 A	04/05/94
		LV 5487 A	10/03/94
		LV 5488 A	10/03/94
		LV 5489 A	10/03/94
		LV 5502 A	10/03/94

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
**PCT/SE 98/01984**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602535 A1	01/02/96	AU 688074 B	05/03/98
		AU 2994895 A	16/02/96
		BR 9508292 A	23/12/97
		CA 2193994 A	01/02/96
		CN 1157614 A	20/08/97
		CZ 9700064 A	11/06/97
		EP 0773940 A	21/05/97
		FI 970102 A	10/01/97
		HR 950401 A	31/10/97
		HU 76642 A	28/10/97
		IL 114477 D	00/00/00
		JP 10504290 T	28/04/98
		NO 970153 A	14/01/97
		NZ 289959 A	26/01/98
		PL 318165 A	26/05/97
		SE 504459 C	17/02/97
		SE 9402510 A	16/01/96
		SK 4897 A	06/08/97
		ZA 9505724 A	15/01/96

---

International application No.  
PCT/SE 98/01984

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		SE 7804231 A	15/10/79
		SU 895292 A	30/12/81
		US 4255431 A	10/03/81
		US 4337257 A	29/06/82
		US 4508905 A	02/04/85
		ZA 7901586 A	30/04/80
<hr/>			